Association Between Pulmonary *Mycobacterium Avium* Complex Infection and Lung Cancer

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Introduction: Patients with lung cancer are sometimes found to have respiratory cultures growing *Mycobacterium avium* complex (MAC). This study describes the clinical, pathologic, and radiographic characteristics of individuals who harbor concomitant lung cancer and MAC.

Methods: Retrospective analysis of patients with positive respiratory cultures for MAC (370 men, 475 women) and with newly diagnosed lung cancer (792 men, 840 women) from 1995 to 2010.

Results: Of the patients with respiratory cultures growing MAC, 8.6% of men and 6.3% of women had lung cancer. Twenty-five percent of patients with lung cancer and 3% with nonbronchiectatic benign lung disease grew MAC from their respiratory cultures. Significantly fewer women with both MAC and lung cancer were smokers than the control group of women with lung cancer and negative MAC cultures (68% versus 89%, $p < 0.01$). Squamous cell carcinoma occurred in 40% of women in the MAC/lung cancer group versus 28% of women in the lung cancer control group. Peripherally located squamous cell carcinomas were found in 71% of the MAC/lung cancer group versus 40% of the lung cancer control group ($p = 0.01$)

Conclusions: The percentage of smokers among women with both MAC and lung cancer was lower than among the lung cancer control group who did not grow MAC. The presence of MAC in respiratory cultures of lung cancer patients was particularly associated with squamous cell carcinomas located in the periphery of the lung. Because MAC typically affects distal airways, this possible association between MAC infection and lung cancer warrants further study.

Key Words: Mycobacterium avium, Lung cancer, Squamous cell, Inflammation, Nonsmokers, Atypical mycobacteria.

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Over the past 20 years, pulmonary infection with *Mycobacterium avium* complex (MAC) has been increasingly recognized as a common infection in patients with otherwise normal lungs, particularly thin, elderly women, and in more traditional hosts such as patients with chronic obstructive pulmonary disease and other structural lung disease.[1,2] The incidence of pulmonary MAC disease in women in the United States has been increasing,[1,2] and this parallels the increase in lung cancer incidence in women in certain regions of the country[3] In a recent population-based study of patients with pulmonary nontuberculous mycobacterial disease, 6.5% of the patients also had lung cancer.[4] At our institution, we have noted an apparent marked increase in the number of lung cancer patients who have been diagnosed with MAC pulmonary infection over the past decade, prompting us to further evaluate the nature and significance of a possible association. Our goal was to begin the process of investigating whether we were simply observing the juxtaposition of two common diseases, versus whether lung cancer may predispose to MAC infection, and/or whether MAC infection may predispose to the development of lung cancer. In the following study, we describe some of the clinical, pathologic, and radiographic characteristics of individuals with concomitant pulmonary MAC infection and lung cancer.

PATIENTS AND METHODS

To identify all patients who had a positive respiratory culture for MAC and lung cancer, a retrospective review was performed through a comprehensive search of the patient databases at Lankenau Medical Center in Wynnewood, Pennsylvania from 1995 to 2010. The names and pathology records of all patients with a diagnosis of lung cancer were retrieved and cross-referenced with a database of all patients with at least one positive respiratory culture for MAC; patients with both diagnoses were included in the "MAC/lung cancer group." Cultures were obtained from sputum or bronchoscopy specimens. Our goal was to include all patients who may have had pulmonary MAC infection, including those with low-grade or subclinical infection; therefore, we included those with positive MAC respiratory cultures, who might be considered to have only "colonization" by the American Thoracic Society/Infectious Disease Society of America guidelines for the diagnosis of pulmonary MAC infection.[5] Of the total of 370 men and 475 women with positive respiratory cultures for MAC, and 792 men

and 840 women with lung cancer, we analyzed the 62 patients with both diagnoses—the MAC/lung cancer group. Of the 1632 individuals with lung cancer, 249 (15%) had mycobacterial cultures sent. Control groups were comprised of the 95 men and 92 women with lung cancer who had negative mycobacterial cultures sent. Smoking histories for all patients were obtained through chart review and, when available, verbal telephone questionnaires. A positive smoking history was defined as at least a 15 total pack per year smoking history. The protocol used in this study was approved by the Main Line Health Institutional Review Board (approval number F/N—R09—2814L).

Pathologic subtypes of lung cancer were recorded by review of pathology reports. In cases in which the tumor was too poorly differentiated to assign a specific lung cancer subtype, but was clearly not a small-cell carcinoma, the designation "non–small-cell lung carcinoma" was assigned.

Lung cancers were classified as central or peripheral, based upon review of chest radiographs and computed tomography (CT) scans by two blinded pulmonologists. Central tumors were defined as those in which the center of mass was within the hilar structures, and peripheral tumors as those in which the center of mass was within the parenchyma, with no contact or minimal contact (in the case of very large tumors) with hilar structures.

Statistical analysis was performed using Fisher's exact test with the calculation of a two-tailed p value for all comparisons. A p value of 0.05 or less was considered significant. Calculations were performed using Graphpad Prism software (GraphPad Prism Software, La Jolla, CA).

RESULTS

There was an overall increase in the number of isolates of MAC from respiratory cultures at our institution throughout the study period from 1995 to 2010. Isolates for MAC far exceeded the number of isolates of pulmonary *Mycobacterium tuberculosis* (MTb), which remained low over the same time period (Fig. 1), an extension of findings from our institution published in 1989.[2]

The overall profile of our study population was as follows: 32 of 370 men (8.6%) and 30 of 475 women (6.3%) with MAC isolated from respiratory cultures also had lung cancer (Table 1). Conversely, 32 of 127 men (25%) and 30 of 122 women (25%) with lung cancer had mycobacterial cultures that were positive for MAC (Table 2). Overall, there were 792 men and 840 women with lung cancer in our database; however, only 249 of 1632 (15%) had mycobacterial cultures sent either via sputum sampling or at the time of bronchoscopy for the diagnosis of their lung cancer or for the workup of pulmonary symptoms. The mean age of men and women in the MAC/lung cancer group was 72 years, versus 71 years for the lung cancer control group. None of the patients with lung cancer had cultures positive for MTb. In a randomly selected sample of 66 patients who underwent bronchoscopy at our institution for nonbronchiectatic benign lung disease, only two patients (3%) had respiratory cultures growing MAC (Table 2). The most common diagnoses among this sample of 66 patients with benign lung disease were interstitial lung disease (26 patients), sarcoidosis (12 patients), and chronic obstructive pulmonary disease (9 patients). Of the two patients in this sample who did grow MAC, one had Wegener's granulomatosis and one had cryptogenic organizing pneumonia.

For the 62 patients in the MAC/lung cancer group, 45 of 62 patients (73%) were diagnosed with MAC and lung cancer within 2 months of each other, thus being considered to have simultaneous infection and lung cancer. For the remainder, 8 of 62 patients (13%) were diagnosed with MAC from

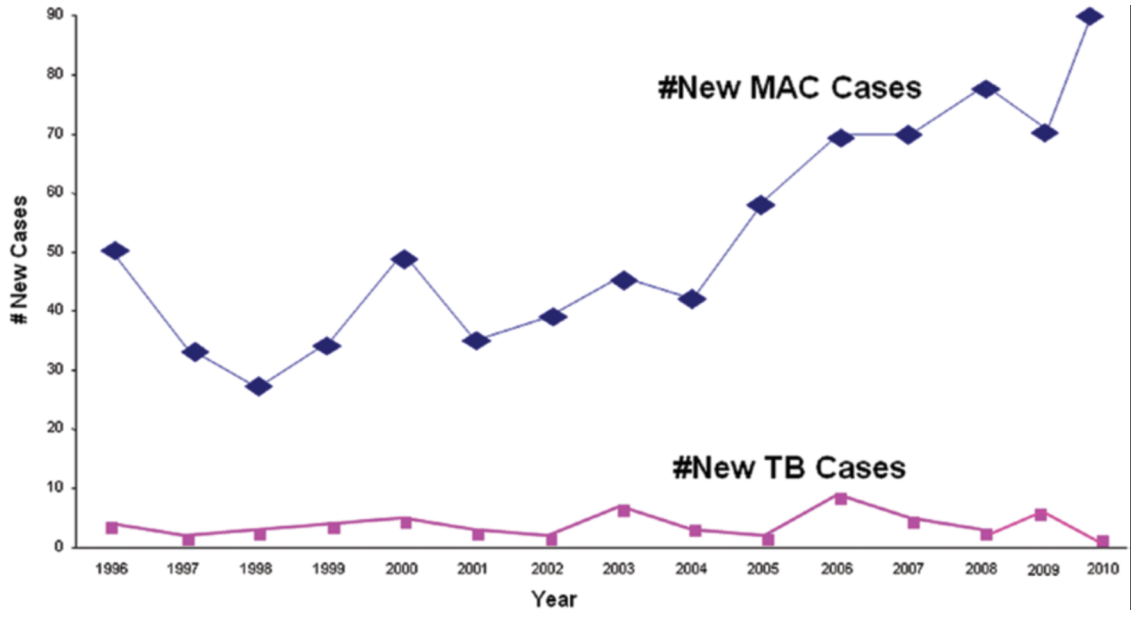

FIGURE 1. Total number of cases of pulmonary infection caused by MAC and TB at Lankenau Medical Center, 1996–2010. MAC, *Mycobacterium avium* complex; TB, tuberculosis.

TABLE 1. Incidence of Lung Cancer Among Patients With MAC Infection, Lankenau Medical Center, 1996–2010

	No. Men (%)	No. Women (%)
MAC+	370	475
MAC+ and lung cancer	32 (8.6)	30 (6.3)

MAC, *Mycobacterium avium* complex.

TABLE 2. Incidence of MAC Infection in Patients With Lung Cancer and Benign Pulmonary Disorders

	No. Men (%)	No. Women (%)	Total
Lung cancer	127	122	249
Lung cancer and MAC+	32 (25)	30 (25)	62 (25)
Benign pulmonary disorder	25	41	66
Benign pulmonary disorder and MAC+	2 (8)	0 (0)	2 (3)

MAC, *Mycobacterium avium* complex.

6 months to 3 years before the diagnosis of lung cancer, and 9 of 62 (14%) were found to have positive MAC cultures at least 2 months after their diagnosis of lung cancer (Table 3).

Smoking histories were obtainable for 28 of 30 women in the MAC/lung cancer group; nine were lifetime nonsmokers (32%), and 19 (68%) were smokers or former smokers. For the 92 women in the lung cancer control group with negative MAC status, 10 (11%) were lifetime nonsmokers and 82 (89%) were smokers or former smokers (Table 4). The difference between these two groups is significant ($p < 0.01$). Smoking histories were obtainable for 29 of the 32 men in the MAC/lung cancer group: four (14%) were lifetime nonsmokers, and 25 (86%) were smokers or former smokers. For the 95 men in the lung cancer control group with negative MAC status, four were nonsmokers (4%) and 91 (96%) were smokers or former smokers ($p = 0.08$) (Table 4).

The MAC/lung cancer group was compared with the lung cancer control group with respect to the specific pathologic subtypes of lung cancer (Fig. 2*A* and *B*). For women, the percentage of squamous cell cancer was 40% in the MAC/lung cancer group versus 28% in the lung cancer control group, a trend that did not reach statistical significance. Overall, no significant differences were found in the subtypes of lung cancer between the two groups.

Because pulmonary MAC infection typically causes pathological abnormalities in the more distal airways, we reviewed the radiographic location of the squamous cell cancers in the MAC/lung cancer group, looking for potential concordance with the location of MAC infection. Of the 28 patients with squamous cell cancer in the MAC/lung cancer group, 20 (71%) had peripheral tumors and eight (29%) had central tumors. Among the 20 MAC/lung cancer patients with peripheral squamous cell tumors, 13 of 20 (65%) were diagnosed with MAC and lung cancer simultaneously; of the remaining patients, four of seven were diagnosed with MAC before the diagnosis of lung cancer. For the 48 patients with squamous cell cancer in the lung cancer control group who had CT scans available for review, 19 (40%) had peripheral tumors and 29 (60%) had central tumors (Figure 3*A*). This propensity for squamous cell cancer in the MAC/lung cancer group to occur in peripheral lung tissue, as compared with the lung cancer control group, is significant ($p = 0.01$).

TABLE 3. Temporal Relationship Between Diagnosis of MAC and Lung Cancer

	MAC Diagnosed Before Lung Cancer	MAC Diagnosed After Lung Cancer	Simultaneous Diagnosis of MAC and Lung Cancer
Number of patients	8	9	45
Percentage of total	13	14	73
Duration (mean)	6 mos–3 yrs (25 mos)	6 mos–4 yrs (15 mos)	Within 2 mos

When diagnosed within 2 mos of each other they were considered "simultaneous."
MAC, *Mycobacterium avium* complex.

TABLE 4. Incidence of MAC in Lung Cancer Patients as a Function of Smoking History

		No. Patients	No. Smokers (% of Patients)	No. Nonsmokers (% of Patients)	Significance (p)
Women	MAC+	28	19 (68)	9 (32)	< 0.01
	MAC−	92	82 (89)	10 (11)	
Men	MAC+	29	25 (86)	4 (14)	= 0.08
	MAC−	95	91 (96)	4 (4)	

MAC, *Mycobacterium avium* complex.

A representative CT scan of one of the patients in our study, who had MAC infection and a peripheral squamous cell cancer is shown in Figure 3*B*. As with most of our study patients, the MAC culture was obtained during bronchoscopy from the same region of the lung as the tumor. Figure 4 is a representative pathologic sample from the lung of one of our study patients, depicting a region of granulomatous inflammation typical of MAC infection immediately adjacent to the squamous cell carcinoma.

DISCUSSION

This study is the first to explore the association of pulmonary MAC infection and lung cancer through an analysis of a large institutional database. Female patients in the MAC/lung cancer group were more likely to be nonsmokers than women with lung cancer and negative mycobacterial cultures. This is particularly noteworthy in light of the disproportionate percentage of nonsmoking women who develop lung cancer. The percentages of nonsmokers in the lung cancer control group of this study roughly matched the percentages of nonsmokers among lung cancer patients in a previous large study conducted in the United States: 7% for men and 15% to 20% for women.[6]

Although the higher percentage of the squamous cell cancer subtype among women in the MAC/lung cancer group,

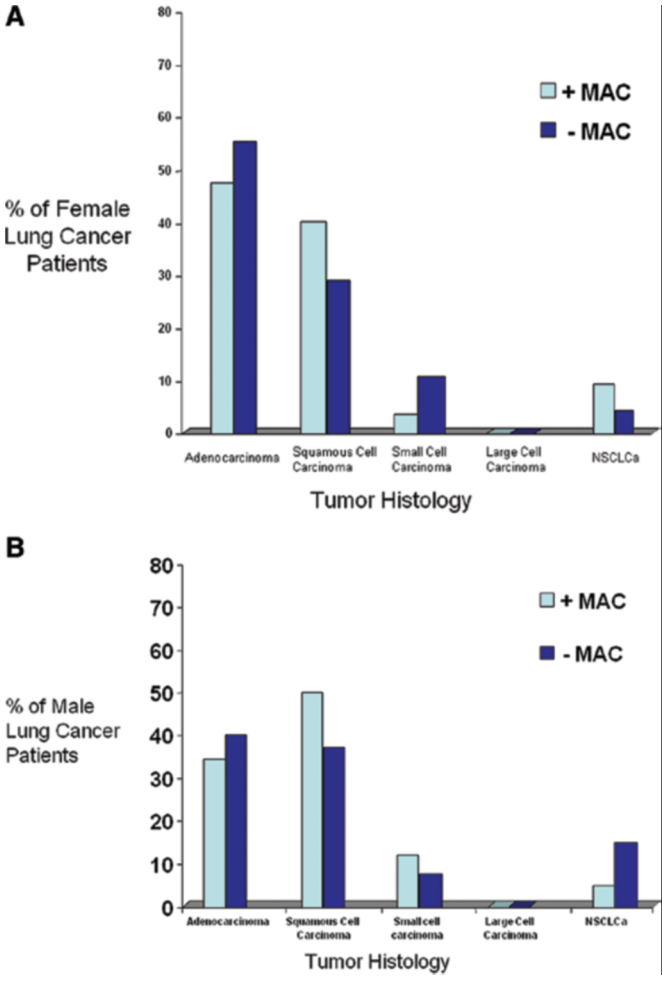

FIGURE 2. *A,* Distribution of different histologic subtypes of lung cancer in female patients with and without MAC infection, and (*B*) in male patients with and without MAC infection. MAC, *Mycobacterium avium* complex.

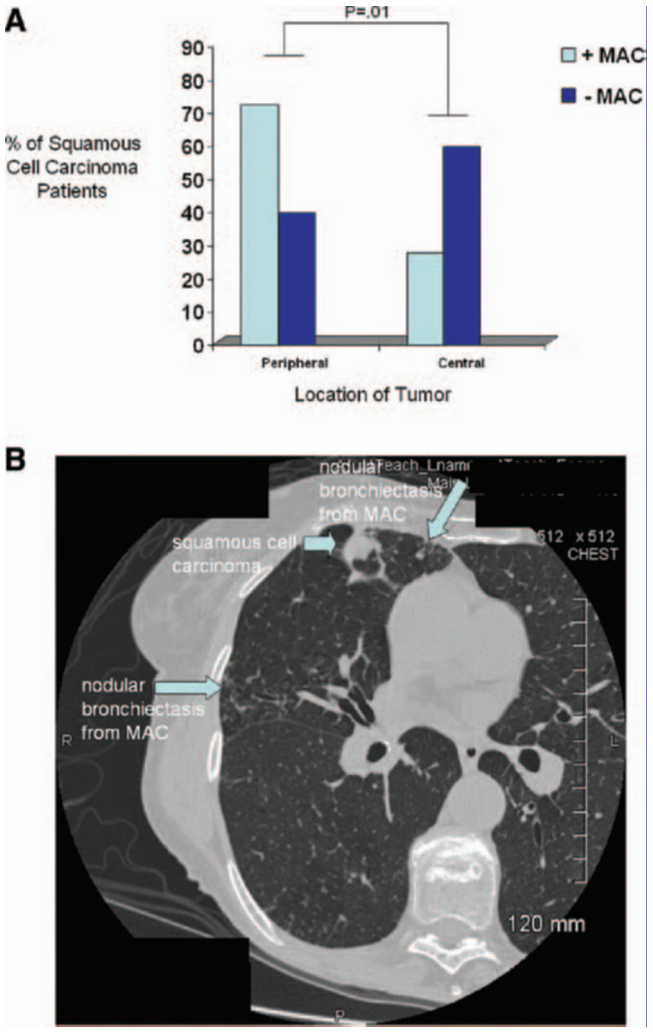

FIGURE 3. *A,* Tumor location in patients with squamous cell carcinoma with and without pulmonary MAC infection. *B,* Computed tomography scan of study patient with MAC and peripheral squamous cell carcinoma. Short arrow indicates location of squamous cell carcinoma. Long arrows indicate areas of bronchiolitis and nodular bronchiectasis typical of MAC infection. MAC, *Mycobacterium avium* complex.

as compared with the lung cancer control group, did not reach statistical significance (40% versus 28%), patients of either sex in the MAC/lung cancer group with squamous cell cancer were more likely to have peripheral lung tumors, compared with the lung cancer control group (71% versus 40%). Recent evidence suggests an increasing tendency for squamous cell carcinomas to arise in peripheral lung tissue, as opposed to the historical findings of squamous cell carcinomas occurring more typically in central airways. In 1996, Quinn et al.[7] published a series demonstrating an increasing percentage of peripheral squamous cell tumors as compared with historical controls from a 1969 series from the Mayo clinic (43%, compared with 31%). This trend is further described in a 2005 study by Brooks et al.[8] who found that 55% of squamous cell carcinomas were peripheral in location.[9] This shift over time in tumor location for squamous cell carcinoma remains unexplained. Because MAC pulmonary infection typically affects the small bronchi and bronchioles in peripheral lung tissue, we postulate that the increasing incidence of this infection could be one of the causes for the increasing tendency for squamous cell carcinoma to occur in peripheral lung tissue.

The possibility of a link between scarring and inflammation from mycobacterial pulmonary infection and eventual development of lung cancer has been previously suggested for humans and already been established by a number of animal studies. For example, pulmonary infection with MTb has long been recognized as a risk factor for lung cancer.[10,11] A recent population cohort study performed in China found an increased risk of lung cancer among individuals with tuberculosis.[12] In a different study, squamous cell metaplasia developed in the lungs of 80% of mice chronically infected with MTb, with some of the lesions showing evidence of malignant transformation.[13] When cells from chronic tuberculous lung lesions without evidence of malignancy were transplanted into syngeneic

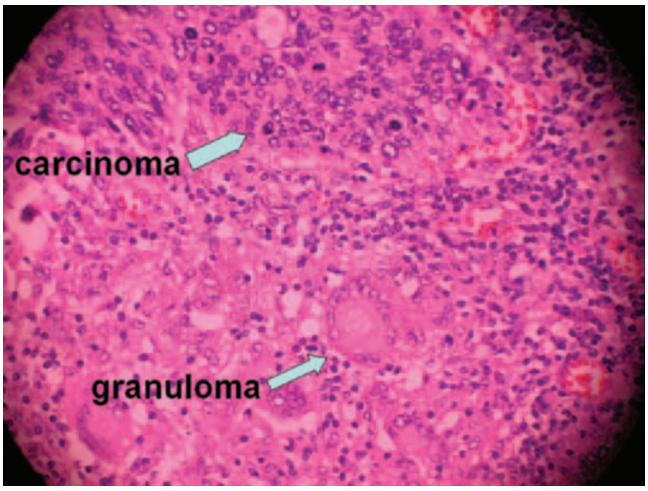

FIGURE 4. Lung pathology specimen of study patient depicting squamous cell carcinoma (upper arrow) adjacent to a region of granulomatous inflammation typical of MAC infection (lower arrow). MAC, *Mycobacterium avium* complex.

mice, 20% of the recipients developed squamous cell tumors. Epiregulin, an epidermal growth factor known to be critical in the development of squamous cell carcinomas, was shown to be up-regulated in the lung tissue of mice after 12 months of tuberculous infection.[13] Furthermore, recent references from Japanese literature suggest the association of mycobacterial disease with squamous cell carcinoma,[14] with these squamous cell carcinomas tending to be peripheral in location.[15,16]

Chronic pulmonary inflammation has been linked to the development of lung cancer in patients with idiopathic pulmonary fibrosis, asbestosis, and interstitial lung disease of other types.[17,18] A variety of studies have shown the association between chronic tissue inflammation or infection and eventual development of the squamous cell carcinoma pathologic subtype in other organ systems.[19–27] A recent report described a patient with interferon γ receptor 2 deficiency, who developed disseminated infection with MAC and other atypical mycobacteria and years later developed diffuse squamous cell carcinoma of the skin.[28]

The persistence of mycobacterial organisms in the lung over months to years causes stimulation of a proinflammatory response that eventually produces extensive damage to surrounding lung and bronchiolar tissue.[29–32] There is growing recognition that chronic inflammatory processes nurture developing malignancies in tissues before overt tumors are established.[33] Local inflammation triggers the release of factors that can support the outgrowth of premalignant cells.[34] Such inflammation-associated immune activation may play a role in combating tumorigenesis, but in some cases may also promote malignant progression by positively selecting for immune escape variants, a process collectively referred to as "immunoediting."[35] The immune environment associated with chronic inflammation likely contains multiple counterbalancing signals including some that are inherently immunosuppressive. Therefore, inflammation may facilitate tumor progression by creating local immune tolerance.[36,37]

The retrospective nature of our study does not allow us to answer the question of timing, that is, does the onset of pulmonary MAC infection significantly precede the development of lung cancer, or does the lung cancer microenvironment create a milieu that promotes the growth of MAC infection in adjacent tissue? Although positive MAC cultures were obtained before the lung cancer diagnosis for some patients in the MAC/lung cancer group, most diagnoses were made simultaneously, with many of the positive MAC cultures in our study having been obtained by bronchoscopy from the same location in the lung as that of biopsy-proven tumors. It is possible that lung tumors can create a microenvironment that supports the establishment of MAC infection. Although tumors usually initiate an inflammatory response in their microenvironment, the ensuing inflammation is always accompanied by anti-inflammation activation. It is advantageous for tumor cells to suppress the immune system, thereby helping them escape immune surveillance. A suppressed immune tumor microenvironment thus promotes tumor progression, and potentially establishes a permissive microenvironment for opportunistic infections such as MAC to take hold and flourish.

In all likelihood, these findings actually underestimate the association of pulmonary MAC infection and lung cancer, as most specimens obtained for cytological or pathologic analysis from patients proven to have lung cancer are not sent for mycobacterial culture testing, hence the opportunity to diagnose subclinical or low-grade infections is lost. Also of note, MAC infections frequently cause nodular bronchiectasis, with continuing chronic inflammation, even if the actual infection is eradicated by the patient's own defense mechanisms or through antibiotic treatment. For these reasons, our lung cancer control group may have included some patients with prior or clinically unapparent pulmonary MAC infections.

Two of the main limitations of this study are the small sample sizes, particularly with regard to the MAC/lung cancer group and the subgroups of smokers versus nonsmokers within this population, and the retrospective nature of the collection of data from a single institution. In addition, the incidence of squamous cell cancer in our female lung cancer control group was somewhat higher than that described in 1999 by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute's lung cancer database (28% versus 21%),[38] allowing for the possibility that larger numbers of patients in both study groups may have resulted in a significant difference in the squamous cell subtype between groups.

Our study also highlights the need for caution when addressing the increasingly common scenarios that unfold when MAC pulmonary infection is identified in patients with suspected lung cancer. Radiographic differentiation between pulmonary MAC infection and lung cancer can be quite challenging, particularly because both can present as nodules, nodular infiltrates, or even cavitary lesions.[39] The array of potential adverse outcomes includes unnecessary diagnostic procedures, including resectional lung surgery for patients with MAC masquerading as lung cancer at one end of the spectrum, versus the possibility that establishing a diagnosis of MAC may abort the diagnostic workup for patients with coexisting lung cancer at the other end of the spectrum. Our observations emphasize that

clinicians must have a heightened index of suspicion for possible coexistent malignancy when MAC is cultured from respiratory specimens in patients with radiographic abnormalities that are also compatible with lung cancer. Patient care would be similarly impacted if the results of our studies indicate that lung tumors establish an environment that promotes MAC infection. Given the potential added physiological burden to cancer patients faced with fighting a serious pulmonary infection while undergoing cancer therapy, these patients should be carefully monitored for early detection of MAC disease.

CONCLUSIONS

In summary, this study describes some of the clinical, pathological, and radiographic characteristics of a group of patients with lung cancer who have had MAC cultured from respiratory specimens. Statistical proof of association and/or causality between MAC pulmonary infection and lung cancer is difficult to establish at this point, particularly because the actual incidence of pulmonary MAC infection is unknown. Although cautious interpretation is warranted, these observations prompt us to postulate such an association, particularly for nonsmoking elderly women and for patients with peripheral lung squamous cell carcinomas. The tendency for lung cancer and MAC infection to occur in the same patient, either simultaneously or sequentially is not without clinical impact; such an association can pose significant diagnostic and therapeutic challenges. These observations underscore the need for further study of the association between pulmonary mycobacterial infections and lung cancer.

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